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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/747,742 | 12/29/2003 | Mark Tawa | TPI-2900C3XC2 | 2066 |

23557 7590 04/02/2007

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

| EXAMINER | |
|---|---|
| ISSAC, ROY P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1623 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/02/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/747,742 | TAWA ET AL. | |
| | Examiner | Art Unit | |
| | Roy P. Issac | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) *3-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/02/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This application claims benefit of 60/486,713 07/11/2003 and claims benefit of 60/459,501 04/01/2003 and claims benefit of 60/456,608 03/21/2003 and claims benefit of 60/456,027 03/18/2003 and claims benefit of 60/441,335 01/21/2003 and claims benefit of 60/437,516 12/30/2002 and is a continuation in part of 10/601,092 06/20/2003 abandoned which claims benefit of 60/390,881 06/21/2002 and claims benefit of 60/426,275 11/14/2002 and claims benefit of 60/427,086 11/15/2002 and claims benefit of 60/429,515 11/26/2002 and claims benefit of 60/437,516 12/30/2002 and claims benefit of 60/456,027 03/18/2003 and is a CIP of PCT/US03/19574 06/20/2003 which claims benefit of 60/390,881 06/21/2002 and claims benefit of 60/426,275 11/14/2002 and claims benefit of 60/427,086 11/15/2002 and claims benefit of 60/429,515 11/26/2002 and claims benefit of 60/437,516 12/30/2002 and claims benefit of 60/456,027 03/18/2003 and said 10/601,092 06/20/2003 claims benefit of 60/390,881 06/21/2002 and claims benefit of 60/426,275 11/14/2002 and claims benefit of 60/427,086 11/15/2002 and claims benefit of 60/428,515 11/22/2002 and claims benefit of 60/437,516 12/30/2002 and claims benefit of 60/456,027 03/18/2003
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which is a CIP of 10/601,092 06/20/2003 ABN which claims benefit of 60/390,881 06/21/2002 and claims benefit of 60/426,275 11/14/2002 and claims benefit of 60/427,086 11/15/2002 and claims benefit of 60/429,515 11/26/2002 and claims benefit of 60/437,516 12/30/2002 and claims benefit of 60/456,027 03/18/2003 and said PCT/US03/41273 12/24/2003 is a CIP of 10/660,202 09/11/2003 which is a CIP of PCT/US03/27772 09/04/2003 which is a CIP of 10/378,956 03/03/2003 which claims benefit of 60/360,768 03/01/2002 and said PCT/US03/27772 09/04/2003 claims benefit of 60/451,213 02/28/2003 and claims benefit of 60/463,962 04/18/2003 and claims benefit of 60/487,064 07/11/2003 and said 10/660,202 09/11/2003 is a CIP of 10/637,829 08/08/2003 which is a DIV of 10/295,995 11/18/2002 PAT 6,699,840 and said 10/295,995 is a CON of 10/232,589 09/03/2002 PAT 6,559,293 which claims benefit of 60/406,974 08/30/2002 and claims benefit of 60/380,288 05/15/2002 and claims benefit of 60/356,764 02/15/2002 and said 10/660,202 is a CIP of 10/449,307 05/30/2003 PAT 7,078,526 which claims benefit of 60/463,962 04/18/2003 and claims benefit of 60/444,315 01/31/2003 and claims benefit of 60/439,282 01/10/2003 and claims benefit of 60/384,152 05/31/2002 and said 10/660,202 is a CIP of 10/601,092 06/20/2003 ABN and claims benefit of 60/451,213 02/28/2003 and claims benefit of 60/463,962 04/18/2003 and claims benefit of 60/487,064 07/11/2003.

### *Election/Restrictions*

Applicant's election without traverse of Group I, claims 1-2 in the reply filed on 10/16/2006 is acknowledged.

Because these inventions are independent or distinct for the reasons set forth in the restriction requirement mailed 9/15/2006 and because the response was made without pointing out any supposed errors, the requirement is deemed proper and is therefore made FINAL.

Therefore, claims 1-2 examined on the merits herein.

### *Claim Objections*

Claims 1-2 are objected to because of the following informalities: Claim 1 recites the abbreviation API and PXRD without defining it in the claims. API is described as "active pharmaceutical ingredient" in the specification. While the abbreviation PXRD is widely used in the specification it is not defined in the specification. Examiner has interpreted PXRD as powder x-ray diffraction. The phrase should be defined in the claims before abbreviation is used. Appropriate correction is required.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 73-78 of copending Application No. 10/551,014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are directed to a propylene glycol solvate of an active pharmaceutical ingredient including olanzapine, and the '014 application claims an olanzapine solvate comprising propylene glycol.

Therefore, claims 1-2 herein are seen to be anticipated by claims 73-78 of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 2 recites the broad recitation the "the API has low aqueous solubility and is selected from the group consisting of steroid drugs", and the claim also recites "the API is olanzapine", and "the API is cortisone acetate" and "the API is naproxen sodium" which is the narrower statement of the range/limitation.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites three PXRD patterns

in claims 2 as (k), (l) and (m). The claim does not recite said patterns in the alternate. As such, it is not clear if the composition comprises all three compounds or whether it is one of the three compounds in the alternate.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a pharmaceutical composition comprising a propylene glycol solvate of olanzapine or cortisone acetate or naproxen, does not reasonably provide enablement for all "active pharmaceutical ingredients". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The instant application is directed to pharmaceutical composition comprising a propylene glycol solvate of any "active pharmaceutical ingredient." The term solvate is broadly defined to include, but not limited to, a compound formed by solvation.

The breadth of the claims:

The instant claim is deemed very broad since it encompasses ***any*** "active pharmaceutical ingredient". The phrase "active pharmaceutical ingredient" encompasses any medicament. This is a very diverse group including small molecule drugs such as aspirin, steroids, statins, as well as peptide drugs such as insulin as well as gene therapy agents.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.S. or equivalent advanced degree.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable

an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses thousands of compositions with varying effects and unknown side effects. As such, each composition will need to be individually evaluated for activity.

The formation of defined crystals is in particular unpredictable. Gavezzotti A. notes that crystal structures are unpredictable. (Acc. Chem. Res. 1994, 27, 309-314; PTO-892). Gavezzotti further gives examples of failed attempts at crystal growth of compounds. (Page 309, Column 2, Paragraph 3). In view of the well accepted skepticism in the filed of crystallography, one of skill in the art will it highly unlikely that ***any*** "active pharmaceutical ingredient", a group that includes any medicament can be made a solvate of propylene glycol. One of skill in the art will view polymorphism as unpredictable, since there are multiple ways to generate them, and their properties as well as how to make them are inherently unpredictable. Rubino et. al. notes that the " accurate prediction of solubilities would most likely require numerous thermochemical data." (PTO-1449 dated 8/10/2004) Such prediction requires that each drug be considered on an individual basis. (Page 145, Column 1, Paragraph 2).

The presence or absence of working examples and the amount of direction or guidance presented:

The applicants disclose examples of propylene glycol solvates of celecoxib, olanzapine, cortisone acetate and naproxen sodium. (Examples 1-6).

All of these are small molecule pharmaceuticals. There are no examples of hydrophilic pharmaceutically active ingredients, or biopolymers that are pharmaceutically active. The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the claim to a propylene glycol solvate to any active pharmaceutical ingredient.

*Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Salem et. al. (International Journal of Pharmaceutics, 141, 1996, 257-259; PTO-892). Salem et. al. discloses polymorphic solvates of terfenadine, an active pharmaceutical ingredient in propylene glycol. (Page 258, Column 1, last paragraph).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunnell et. al. (U.S. Patent No. 5,736,541; PTO-892) in view of Kaplan et. al. (U.S. Patent No. 3,970,651; PTO-892).

The '541 patent discloses polymorph crystals of olanzapine. (Abstract). Exmaples of the formation of olanzapine is disclosed. (Columns 10-11, Examples 1-4).

The '541 does not expressly disclose polymorphs formed by solvation with propylene glycol.

Kaplan et. al. discloses the use of propylene glycol for the formation of polymorphs of active pharmaceutical ingredients, cephalosporin. (Abstract).

Kaplan et. al. further discloses that the biologically inert propylene glycol produced solvate of the active pharmaceutical ingredient which exhibited crystalline quality. (Column 3, lines 20-32; Column 1, lines 45-65). Furthermore, Kaplan discloses propylene glycol solvates to be substantially free of impurities, and discloses crystallization using propylene glycol as a method of purification as well. (Column 3, lines 2-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polymorph of olanzapine using propylene glycol because the '541 patent discloses the formation of polymorphs by olanzapine and propylene glycol is well known for its effects in the formation of polymorphs of active pharmaceutical ingredients. Furthermore, it is considered within the capabilities of one of skill in the art to select the appropriate range of solvents, carriers and excipients. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). Note that it is well settled that, merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket,* 33 USPQ 33 (C.C. P.A. 1937). *In re Russell*, 439 F.2d 1228, 169 U.S. P.Q. 426 (C.C. P.A 1971).

One of ordinary skill in the art would have been motivated to make propylene glycol solvate of olanzapine because it is a biologically inert solvent that is well known to give crystalline product that is substantially free of impurities.

Therefore, one of ordinary skill in the art would have reasonably expected that the use of propylene glycol would have resulted in solvates of olanzapine or cortisone or naproxen with substantially similar or better qualities.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Roy P. Issac
Patent Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623